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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/553,722 | 07/10/2006 | Rosanne M Crooke | BIOL0004USA | 6604 |
| 72984 | 7590 | 10/31/2007 | | |
| JONES DAY for Isis Pharmaceuticals, Inc. 222 East 41st Street New York, NY 10017-6702 | | | EXAMINER GIBBS, TERRA C | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|-------------------------------|-------------------------------|--|
| Office Action Summary | Application No. 10/553,722 | Applicant(s) CROOKE ET AL. | |
| | Examiner Terra C. Gibbs | Art Unit 1635 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 61,65-70,72-76 and 84-99 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 61,65-70,72-76 and 84-99 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>August 14, 2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed August 14, 2007.

Claims 62-64, 71, and 77-83 have been canceled. Claims 61, 65, 66, 70, 72, and 73 have been amended. New claims 84-99 are acknowledged.

Claims 61, 65-70, 72-76, and 84-99 are pending.

Claims 61, 65-70, 72-76, and 84-99 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement filed August 14, 2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Priority

It is noted that in the previous Office Action mailed February 14, 2007, the instant application was afforded priority to July 10, 2006, which is the filing date of the instant application because support for a method of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that

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specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III was only found in the instant application, but not in any application that Applicants claimed priority to.

Response to Arguments

In response to the Examiner's grant for priority, Applicants argue that support for the methods as claimed in the instant application can be found throughout the specification of International Application PCT/US04/10946. More specifically, Applicants contend that support for the methods as claimed can be found at pages 29, 102, and 103 of the International Application. In view of this support, Applicants argue that the instant application should be afforded priority to International Application PCT/US04/10946, filed April 15, 2004.

Applicant's arguments and contentions have been fully considered, and are found persuasive. It is noted that the Examiner is affording the instant application priority to April 15, 2004, which is the filing date of PCT/US04/10946 since it appears that the International Application has support for the instantly recited claims.

Double Patenting

In the previous Office Action mailed February 14, 2007, claims 61-83 were provisionally rejected under the judicially created doctrine of double patenting over claims 23, 38, 39, 45-62 and 64 of copending Application No. US Publication No. 20040208856 ('856). **This rejection is moot** against claims 62-64, 71, and 77-83 in

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view of Applicant's Amendment filed August 14, 2007 to cancel these claims. **This rejection is maintained** against claims 61, 65-70, and 72-76 for the reasons of record set forth in the previous Office Action mailed February 14, 2007.

Response to Arguments

In response to this rejection, Applicants request that this rejection be held in abeyance until the claims are otherwise in a condition for allowance. This request has been considered and it is noted that that this rejection will be held in abeyance until the claims are found to be allowable.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed February 14, 2007, claims 61-83 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising the intraperitoneal injection of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:11), does not reasonably provide enablement for methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising any route of administration of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4). **This rejection is moot** against claims 62-64, 71,

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and 77-83 in view of Applicant's Amendment filed August 14, 2007 to cancel these claims. **This rejection is withdrawn** against claims 61, 65-70, and 72-76 in view of Applicant's Remarks filed August 14, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Remarks that the claims are adequately enabled by the specification since Applicants have demonstrated that the systemic delivery (e.g. intraperitoneal) of antisense compounds targeted to nucleic acid molecules encoding apolipoprotein C-III ameliorates hepatic steatosis, lowers liver tissue triglyceride levels, and reduces adipose tissue in an animal.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed February 14, 2007, claims 61-83 were rejected under 35 U.S.C. 102(b) as being anticipated by Crooke, RM (Expert Opinion in Biol. Ther., July, 2005 Vol. 5:907-917. **This rejection is moot** against claims 62-64, 71, and 77-83 in view of Applicant's Amendment filed August 14, 2007 to cancel these claims. **This rejection is withdrawn** against claims 61, 65-70, and 72-76 in view of the fact that the Examiner has afforded the instant application priority to April 15, 2004, which is the filing date of PCT/US04/10946.

After careful reconsideration of the claims, a new ground(s) of rejection is made of record as detailed below:

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 61, 65-70, 72-76, and 84-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shachter, N. (Applicant's Reference BF on the Information Disclosure Statement filed August 14, 2007), in view of GenBank Accession No. NT_035088 (Applicant's Reference BL on the Information Disclosure Statement filed August 14, 2007), Jong et al. (Arterioscler Thromb Vasc Biol., 1999 Vol. 19:472-484), Senior, K. (Drug Discovery Today, 2002 vol. 7:840-841, Applicant's Reference BE on the Information Disclosure Statement filed August 14, 2007), and Monia et al. (Applicant's Reference AE on the Information Disclosure Statement filed August 14, 2007).

Claim 61 is drawn to a method of ameliorating hepatic steatosis in an animal comprising administering an antisense compound that is 100% complementary to a nucleic acid encoding apolipoprotein (SEQ ID NO:4) and inhibits the expression of apolipoprotein C-III, so that hepatic steatosis is ameliorated. Claims 65-69 and 84-91 are dependent on claim 61 and include all the limitations of claim 61 with the further limitations wherein the antisense is single-stranded; wherein the antisense comprises at least one modified internucleoside linkage, sugar moiety, or nucleobase; wherein a gap segment of linked 2'-deoxynucleotides positioned between a 5' wing segment of linked nucleosides and a 3' wing segment nucleosides, wherein each nucleoside of each wing segment comprises a modified sugar moiety; and wherein the antisense is delivered by parenteral or subcutaneous administration. Claim 70 is drawn to a method of lowering liver tissue triglyceride levels in an animal comprising administering an antisense compound that is 100% complementary to a nucleic acid encoding apolipoprotein (SEQ ID NO:4) and inhibits the expression of apolipoprotein C-III, so that liver tissue triglyceride levels are lowered. Claims 72-76 and 92-99 are dependent on claim 70 and include all the limitations of claim 70 with the further limitations wherein the antisense is single-stranded; wherein the antisense comprises at least one modified internucleoside linkage, sugar moiety, or nucleobase; wherein a gap segment of linked 2'-deoxynucleotides positioned between a 5' wing segment of linked nucleosides and a 3' wing segment nucleosides, wherein each nucleoside of each wing segment comprises a modified sugar moiety; and wherein the antisense is delivered by parenteral or subcutaneous administration.

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Shachter teaches apolipoprotein C-III as an important modulator of lipoprotein in metabolism (see Abstract). Specifically, Shachter teaches that the variation in the expression of apolipoprotein C-III has an important role in hypertriglyceridemia (see Abstract) and an important role for apolipoprotein C-III in elevating plasma triglycerides levels has been shown (see page 301, first column).

Shachter do not teach administering to an animal, an antisense compound that is 100% complementary to a nucleic acid encoding apolipoprotein (SEQ ID NO:4).

GenBank Accession No. NT_035088 teaches a Homo sapiens chromosome 11 reference genomic contig that comprises SEQ ID NO:4 of the instant invention.

Jong et al. teach, "Human apoCs have been demonstrated to have distinct effects on the major metabolic pathways in lipoprotein metabolism, implying that changes in human APOC gene expression may play an important role in the etiology of human hyperlipidemias" (see page 479, last paragraph)..

Senior teaches antisense inhibitors as effective treatment approaches for hypercholesterolaemia (see Abstract). Particularly, Senior teach that antisense oligonucleotides can be delivered to *in vivo* mouse models of hypercholesterolaemia and plasma triglyceride levels can be decreased (see entire article, especially at Figure 1 and page 841, first column).

Monia et al. teach antisense oligonucleotide compounds can be synthesized to a preferred gene of interest to modulate gene expression. Monia et al. teach that the antisense oligonucleotides can be delivered to animal cells *in vivo*. Monia et al. teach that antisense can be delivered by parenteral or subcutaneous administration. Monia et

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al. further teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Monia et al. teach antisense oligonucleotides with phosphorothioate modified backbones... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties... with modified nucleobases, such as 5-methylcytosine... with a gap segment of linked 2'-deoxynucleotides positioned between a 5' wing segment of linked nucleosides and a 3' wing segment nucleosides, wherein each nucleoside of each wing segment comprises a modified sugar moiety (see Example 5 and Table 1, for example). Monia is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligonucleotides to target any known gene.

It would have been *prima facie* obvious for one of ordinary skill in the art to devise a method of ameliorating hepatic steatosis in an animal or a method of lowering liver tissue triglyceride levels in an animal comprising administering an antisense compound that is 100% complementary to a nucleic acid encoding apolipoprotein (SEQ ID NO:4) using the teachings of Shachter, the motivation of Jong et al., and following the methods taught by Senior et al., and Monia et al. It would have been *prima facie* obvious for one of ordinary skill in the art to target a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4) using the sequence taught by GenBank Accession No. NT_035088.

One of ordinary skill in the art would have been motivated to devise a method of ameliorating hepatic steatosis in an animal or a method of lowering liver tissue

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triglyceride levels in an animal since Shachter taught that modulating apolipoprotein C-III expression effects plasma triglyceride levels, which plays a critical role in clinical hypertriglyceridemia. One of ordinary skill in the art would have been motivated to use an antisense oligonucleotide targeted to a nucleic acid molecule encoding apolipoprotein C-III since Jong et al. taught that APOC gene expression possibly plays an important role in the etiology of hyperlipidemia in humans. Further, one of ordinary skill in the art would have been motivated to use an antisense oligonucleotide targeted to a nucleic acid molecule encoding apolipoprotein C-III since Senior taught antisense inhibitors as effective treatment approaches for disease conditions involving elevated triglyceride levels, such as high cholesterol. One of ordinary skill in the art would have been motivated to use an antisense oligonucleotide targeted to a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4) since the human sequence was known in the art at the time of filing to be a known target sequence for modulating apolipoprotein C-III expression and Monia et al. teach antisense oligonucleotide compounds can be synthesized to a preferred gene of interest to modulate gene expression. One of ordinary skill in the art would have been motivated to have the antisense oligonucleotide targeted to a nucleic acid molecule encoding apolipoprotein C-III comprise at least one modified internucleoside linkage, sugar moiety, or nucleobase since Monia et al. taught that modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

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One of ordinary skill in the art would have expected success at devising a method of ameliorating hepatic steatosis in an animal or a method of lowering liver tissue triglyceride levels in an animal comprising administering an antisense compound that is 100% complementary to a nucleic acid encoding apolipoprotein (SEQ ID NO:4) because the prior art taught the successful delivery of an antisense to an *in vivo* mouse model for the treatment of hypercholesterolaemia, which involves modulating triglyceride levels.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information

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for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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tcg

October 28, 2007

/Terra Cotta Gibbs/